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June 1, 2005

Dr. Examiner of the US Patent Application (Appl No.: 10/810.296),
The United States Patent and Trademark Office (USPTO),
Commissioner for patents,
P.O. Box 1450,
Alexandria, VA 22313-1450

Dear Dr. Examiner:

I am an applicant of the US patent (Aplication No.: 10/810,296, Filing date: 03/27/2004). Please find enclosed the letter dated 08/06/2004 from the USPTO.

I have enclosed an offprint of the review article entitled "Analytical Methods of Atherosclerosis Research" published in Trends In Atherosclerosis Research, Nova Biomedical Book. I have just received the offprint from Nova science publishers Inc. The equation (A) of the page No. 14 of the above-mentioned application is the equation (33) of the page No. 296 of the article. In addition, the application also involves the analytical examples of the page No. 296-297 and the remark of page No. 306-307 of the article. This article is the reference [No. 1] of the application.

I have also enclosed an offprint of the review article entitled "Analytical Methods of Atherosclerosis" published in Atherosclerosis 159 (2001) 1-7. This article is the reference [No. 2] of the application.

I appreciate it if I may receive the US patent of the application from the USPTO soon.

Please contact me at phone No.: 1-774-2393884, fax No.: 1-508-8310592 or e-mail: xingfwang@gmail.com if there are any questions regarding the above-mentioned matter.

Thank you for your consideration.

Sincerely

Xingfa Wang

Xing Fa Wang, Ph.D.

Encl.: Letter & articles.

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Chapter XI

ANALYTICAL METHODS OF ATHEROSCLEROSIS RESEARCH

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INTRODUCTION

Atherosclerosis is a progressive disease characterized by the thickening, hardening and loss of elasticity of inner arterial walls. The pathologic process of this disease underlies most coronary heart disease (CHD) and strokes. Atherosclerosis has plagued Western societies and is responsible for over half of the deaths among the elderly worldwide. As a result, the disease has been the subject of research for over two centuries [1-37]. Research has intensified worldwide because atherosclerosis is becoming the biggest killer among otherwise healthy individuals. The World Health Report estimated that atherosclerosis would be the greatest single disease burden worldwide by 2020 [38]. The direct and indirect costs associated with the disease have been estimated at $111.8 billion every year in the United States alone [39]. Despite our growing knowledge of the cause of atherosclerosis, the prevalence of the disease has yet to be reversed.

Over the past five decades, lipid-lowering therapy has dominated strategies for preventing and treating atherosclerosis [20,40-43,68,69]. The lipid hypothesis suggests that the elevated level of low-density lipoprotein (LDL) or cholesterol in human blood is the primary cause of the disease. It is reported that there are about 55 million American adults who have elevated levels of LDL that warrant intervention [44]. However, clinical evidences indicate that many individuals in the United States develop CHD in the absence of abnormalities in lipoprotein profile [37]. Recently, a number of studies focused on

inflammation as a primary cause in atherosclerosis [37,45-48]. The inflammation hypothesis emphasizes that macrophages have essential functions in all phases of atherosclerosis.

From epidemiological and clinical studies, numerous factors have been linked to the disease. Contributory factors that have been linked to atherosclerosis include elevated LDL level, reduced high-density lipoprotein (HDL) level, hypertension, smoking, family history, systemic inflammation, infectious agents, age, high-fat diet, nutritional status, immunity, obesity, hormones, lack of exercise and emotional stress [20,32]. Additionally, clinical and experimental evidences have associated elevated heart rate with the disease [49,50]. However, the presence of any combination of these factors will not guarantee atherosclerosis nor will their absence necessarily indicate prevention from the disease. Furthermore, these factors affect the entire body and cannot account for the extreme localization associated with atherosclerotic lesions.

The objective of this chapter is to resolve some of the fundamental challenges in studying atherosclerosis by creating the Mass Transfer Flux Model and the Lesion Adherence Model using analytical methods. The Mass Transfer Flux Model is comprised of a bioheterogeneous reaction model, a natural convection model and a boundary value model, and is used to unite atherosclerotic risk factors with potential clinical applications. The Lesion Adherence Model is comprised of a thermodynamics model and a boundary value model, and is used to further the understanding of atherosclerotic mechanisms. We aim to show that analytical methods can play a crucial role in the study of atherosclerosis when the reward of prevention and the potential for regression is maximal.

1. Modeling Atherosclerosis

As with many major human diseases, the mechanisms involved in atherosclerosis are complex and multifaceted. The characteristic evolution time of this progressive disease is slow, and clinical symptoms only manifest after years of development. These conditions make atherosclerosis especially difficult to study *in vivo*. For these reasons, we must rely on models of the disease's processes. Atherosclerotic models permit the simulation of cause and effect which is used in place of a real atherogenic event to draw inferences regarding the response of the event to changes in various input conditions.

Take an atherogenic process to be the first diagramed box in Figure 1a. Inputs to this box are determined by environmental features including interactions among the blood constituents such as lipoproteins, monocytes, and platelets, characterization of local hemodynamic flow, and reactionary responses by arterial endothelium cells at the plasma-endothelial interface. The output corresponds to the various manifestations of the disease that result from the atherogenic process with the given the input conditions. These manifestations may include lesion growth rate, size, shape, composition, location, and proclivity to rupture. The manifestations may be regarded as a collection of ultimate clinical goals that include prediction of disease risk level and primary cause of disease, establishment of therapeutic treatment, and assessment of treatment efficiency.

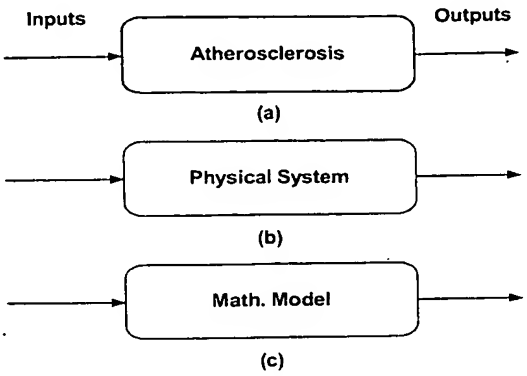

Figure 1: The philosophy of modeling atherosclerosis

To reveal the atherogenic event, we replace atherosclerosis with a physical system (Figure 1b) in which the system is defined for some definite region of space. We then assume that the outputs from the system are approximately the same as the outputs that would have resulted had the real event been in the first atherosclerosis box. All the features of the real atherogenic event will not be present in the physical system, but using a reliable hypothesis for the atherogenic event and a set of efficient parameters as inputs for the system, we can equate the two box processes.

In order to truly model a process, we need to replace the physical system with a series of mathematical models (Figure 1c) by imposing entity balance and conservation principles of mass, momentum and energy to the physical system and creating a set of mathematical variables as inputs to the model. The outputs of the mathematical model are the ultimate goal of modeling and are determined by solving a system of differential equations. We will take the above-mentioned approach to modeling atherosclerosis.

Entity Balance

The entity balance of a general system is expressed as

$$\text{Input} + \text{Generation} = \text{Output} + \text{Accumulation} \tag{1}$$

in which the input is defined as quantities cross the system boundary from the outside to the inside in a time interval Δt, and the output is defined as the converse. The accumulation is defined as the difference between the starting quantities and the ending quantities within the system in this time interval. The generation is defined as the quantities that are produced within the system in this interval. Conservation principles of mass, momentum and energy govern the transport processes without either creating or destroying the quantities. The entity balance has the form

$$\text{Input} = \text{Output} + \text{Accumulation} \tag{2}$$

In a steady-state process, the quantities do not change with time. For processes of rates, the entity balance has the form

$$\text{Input Rate} + \text{Generation Rate} = \text{Output Rate} \tag{3}$$

Continuity assumes that the fluid has a unique value at a given point and time. We will consider our models to be a conservative, steady and continual system.

2. THEORIES OF ATHEROSCLEROSIS

Many theories for the origin and development of atherosclerosis have been postulated over the years. However, none of them gives a complete and satisfactory picture of the mechanism of the disease. Several major theories are summarized below, but current views are far less categorical and usually incorporate elements from any number of these hypotheses.

Thrombogensis

This theory states that mural thrombosis is the essential and primary step in atherogenesis and was first proposed by Rokitansky in 1852 [2]. After thrombi forms in the vessels, they are incorporated within the intima. A sequence of reactions including the migration and proliferation of smooth muscle cells takes place, which finally leads to the atherosclerotic lesion [12].

Lipid Theory

This theory regards atherosclerosis as a consequence of defects in the metabolism of cholesterol and other lipids and was first noted by Anitschkow in 1913 [4]. The theory points to high serum cholesterol or LDL levels as a major risk factor of the disease [20,40-43]. Low-density lipoprotein (LDL), a major cholesterol-carrying lipoprotein in the serum, has been recognized by the National Cholesterol Education Program (NCEP) as the major atherogenic lipoprotein [43].

Inflammation Theory

This theory was first proposed by Virchow in 1856 [3] and emphasizes an early event in atherosclerosis as an inflammatory response to an injured arterial wall. Based on the inflammation theory, Ross and Glomset in 1973 proposed the response-to-injury hypothesis [10]. The hypothesis is based on the idea that the functioning of the endothelium is changed locally due to mechanical damage imparted on the endothelium. These changes lead to secretion of platelet-derived growth factor, migration and proliferation of smooth muscle cells in the intima and further endothelial damage. As a consequence, atherosclerosis arises as an exaggerated response to the initial injury to the endothelial layer of the vessel wall, which

leads to an atherosclerotic lesion. Current research emphasizes macrophages as having essential roles in all phases of the disease [37,45-48].

Flow Theory

This theory relates atherosclerosis to the effects of the bloodstream on the arterial wall. Experimental findings reveal that lesions are often found near branch sites, curved vessels, bifurcations of large arteries, and other regions of perturbed blood flow. A number of hypotheses arise from the flow theory [6-8,13-14,18,21,35,51-56]:

Stagnation Point Hypothesis

Proposed by Fox and Hugh in 1966 [6], this hypothesis states that the localization of atheroma is characterized by boundary layer separation where secondary flow and blood flow perpendicular to the wall may occur. According to this theory, stagnation points where blood components spend longer time than normal or where the flow causes increased transport of blood components may be the cause of atherosclerosis.

High Wall Shear Stress Hypothesis

Proposed by Fry in 1968 [7], this hypothesis focuses on the notion that shear forces caused by blood flow passing by the endothelial wall may be so high that the vessels become damaged and the subendothelium exposed, thus leading to an atherosclerotic event.

Low Wall Shear Stress Hypothesis

Caro *et al* in 1969 [8] proposed that atherosclerotic lesions occur in areas experiencing low and fluctuating wall shear stress. This hypothesis views mass diffusion as the mechanism of LDL transport to the vessel wall, which increased at low local shear rates.

Diminished Lateral Pressure Hypothesis

Texon in 1980 [13] developed a concept called the hemodynamic basis of atherosclerosis. This hypothesis states that atherosclerotic lesions occur at the segmental zones of diminished lateral pressure generated by the flowing blood in the region of arterial bifurcations, curvatures or branching called the lesion-prone sites.

Convection-Diffusion Hypothesis

When endothelial wall lining is damaged, platelets adhere to the subendothelium and form thrombi. This theory focuses mainly on the platelet-vessel wall interaction caused first

by convective and diffusive transport of platelets to the vessel wall, then adhesion to the vessel, and finally aggregation of platelets to form a thrombus [71].

In devising these theories of atherosclerosis, three well-established investigative methods have been used. The oldest method relies on many valuable observations of atherosclerotic plaques in autopsies within various age groups and with diseases such as hyperlipidemia, diabetes and hypertension. The second method is the use of epidemiological studies to explain factors that promote or protect people from atherosclerosis. The third method utilizes classical experimental pathology to study sequences of lesion development or regression in animal models of atherosclerosis.

While each of the above theories has its own substantiating clinical or experimental evidences, they are not mutually exclusive, and they only attempt to explain a part of the many aspects of atherosclerosis. Even though these theories and methods are worthy of investigation and each one has contributed to an increased understanding of atherosclerosis, little substantial progress has been made in the prevention or regression of the disease [38]. Atherosclerosis is a multifactor disease with many risk factors. Analytical models are useful in studying atherosclerosis because the models can explore interactions among numerous factors at the same time, thus providing a better description of the disease.

3. Biological Environment of Atherosclerosis

The hypothesis of atherogenesis relies heavily on the understanding of atherosclerotic mechanisms and the evolution of atherosclerotic lesions. Atherosclerotic events may be considered to be biological responses of endothelial cells to blood constituents and local blood flow on a plasma-endothelial interface at the arterial wall. Thus, we must first consider the biological factors and their manifestations in atherosclerosis.

3.1. Blood Constituents

The blood is a complex suspension of red and white corpuscles, platelets and lipid globules dispersed in a colloidal solution of proteins. The blood is roughly 45% cells, the largest of which are red blood cells (~5 x 10^6 per mm^3). The non-cellular fluid is the plasma, which consists of 95% water and 5% proteins. Main players of atherosclerosis in the blood include the following:

Low-Density Lipoproteins (LDL)

LDL is a major carrier of cholesterol in the blood. High serum LDL has been identified to be a major risk factor of atherosclerosis [20, 40-43,68,69]. The sizes of LDL particles range from 21 to 25 nm in diameter [57]. LDL size is significant to atherogenesis because LDL particles penetrate through endothelial cells and accumulate in the subendothelium where they can initiate an atherosclerotic event [20]. In contrast to LDL however, high-density lipoproteins (HDL) seem to provide protection from the disease.

Monocytes

The circulating leukocyte-monocyte is the first cell to adhere to the intact endothelium. It eventually migrates between endothelial cells, locates itself in the subendothelial space, and transforms into the foamy macrophage through the ingestion of lipids [37,47]. The binding and recruitment of circulating leukocyte-monocytes to the arterial endothelium is considered a fundamental step in developing an atherosclerotic lesion, in particular those that go on to develop plaque rupture. Ruptured lesions typically have a large necrotic core and a disrupted fibrous cap infiltrated by macrophages. A number of research studies [37,45-48] suggest that monocyte-macrophages have essential functions in all phases of atherosclerosis, from development of fatty streaks to processes that ultimately contribute to plaque rupture and myocardial infarction.

Platelets

The minute, nonnucleated, disk-like cytoplasmic body functions to promote blood clotting. Platelets are the source of numerous pro-inflammatory mediators and can initiate the vascular phase of an acute inflammatory response.

3.2. Arterial Wall

The arterial wall is composed of a number of successive concentric layers. The *tunica intima* is the innermost arterial layer. It contains a monolayer of endothelial cells lying on a basal lamina. The endothelial cells are aligned according to the streamlines in the blood vessel and are in constant contact with the blood. At areas of irregular blood flow of lesion-prone sites, e.g. bifurcations, the endothelial cell shape is irregular. High shear regions tend have more endothelial cells that are elongated whereas low shear regions tend to have rounder endothelial cells. Most of the resistance to blood flow in the artery is due to the endothelial layer of the intima. A thin sub-endothelial layer, which includes longitudinal collagen fibers, elastic fibers, and smooth muscle cells, follows the basal lamina. The internal elastic lamina separates the tunica intima with the tunica media. The *tunica media* is composed of 10 to 60 layers of smooth muscle cells surrounded by a fine network of collagen and elastic fibers. The external elastic lamina separates the tunica media and the tunica adventitia. The *tunica adventitia* is composed of elastic fibers that intermingle with compact collagen fibers. The inner elastic fibers running longitudinally while the outer elastic fibers run circumferentially. The outermost region of the adventitia is composed of loose connective tissue.

3.3. Lesions Types

To successfully model atherosclerosis, we must understand the morphology of the disease. Atherosclerotic lesions are never constant but are subject to change as the disease progresses through different stages. The following stages defined by the American Heart Association (AHA) are used to categorize the evolution of atherosclerotic lesions [1].

Isolated Foam Cellsh

The earliest stage is the intimal thickening due to macrophages that are overloaded with lipid droplet inclusions called foam cells. Groups of foam cells are more frequent in eccentric

thickening while isolated foam cells are more common in diffuse thickening. The foam cells occur in half of infants in the first seven months of life.

Fatty Streaks

Fatty streaks start from simple deposition of low-density lipoproteins (LDL) onto the aortic endothelium. LDL is transported to the intima through the endothelium. The LDL undergoes oxidative modifications to become Ox-LDL, which is potentially cytotoxic. Meanwhile, monocytes from the blood stream migrate to the intima and become activated macrophages. These macrophages, as well as migrating smooth muscle cells from the media, take up the Ox-LDL in large amounts and become the lipid-laden foam cells of the first stage. The conglomeration of foam cells, smooth muscle cells, and extracellular tissue is the fatty streak and has a yellow appearance due to the accumulation of lipids. Fatty streaks occur at a universal age of ten, but progress to more advanced stages at different rates in different people.

Preatheroma

Preatheroma is a link between the fatty streak and the atheroma and occurs in the middle of the second decade of life and only in eccentric thickening. The preatheroma is characterized by multiple small pools of particles clustered in the deep intima layer that separate and displace some smooth muscle cells.

Atheroma

An atheroma is an eccentric thickening that metamorphosed into an advanced atherosclerotic lesion due to increased accumulation and retention of lipid. The extracellular lipid is concentrated at the core and replaces much of the musculoelastic intima layer. The macrophage foam cells and lipid-laden smooth muscle cells are layered above the core.

Fibrous Plaques

Fibrous plaque, also called atheromatous, fibrofatty or fibrolipid plaque, is the characteristic plaque of more advanced atherogenesis. The plaque consists of a mass of lipid encapsulated in the intima, separated from the lumen by a cap of fibrous tissue. This lesion contains not only more smooth muscle cells, but also more collagens, elastic tissues, mononuclear phagocytes, and intracellular and extracellular lipids. This is also the stage of the disease characterized as arteriosclerosis or arterial hardening because much of the elasticity of the inner arterial walls is lost.

Complex Lesions

The final stage is the *complex lesions* that are of thrombus formation with deposits of fibrins and platelets. Complex lesions no longer have the endothelium covering and blood platelets are able to adhere to the subendothelial tissue leading to the formation of a thrombus. Complex lesions may hemorrhage and have the same white appearance as the fibrous plaques.

3.4. Hypothesis of Atherosclerosis

From the previous discussions, we propose that the mass transfer flux of LDL and monocytes in the blood to the arterial endothelium at lesion-prone sites is a primary cause of

atherosclerosis. We will motivate this hypothesis by using analytic methods presented in th chapter.

4. PHYSICAL SYSTEMS

The second phase of modeling atherosclerosis is to translate the biological environment and parameters that affect the disease into physical parameters founded on physical principles like fluid dynamics and thermodynamics. In particular, we aim to model two processes in atherosclerosis: (1) the transport of atherogenic constituents such as LDL from the blood to the arterial endothelium and (2) the interaction of transferred constituents with the arterial wall which causes lesions to form. A bioheterogeneous model and a natural convection model describing mass transfer flux of atherogenic constituents will be used to model the first process. A thermodynamics model describing lesion adhesion will be used to model the second process. Some scientific terms and quantities are employed for the physical system, and they must first be properly defined and understood. Refer to references [58-62] for further information of these terms and quantities.

4.1. Hemodynamic Behavior

Under certain physiological conditions, blood exhibits *laminar flow* in which parallel streamlines of fluid governed by viscous forces slip by one another in an orderly manner. In a circular tube such as the artery, laminar flow may exhibit a parabolic-shaped profile. The center of the laminar flow profile has the maximum velocity. At the wall of the tube, the velocity of the flow is zero meaning that the layer of fluid next to the wall remains fixed. This condition of no velocity at the wall is also referred to as the *no-slip condition*.

Under other conditions, blood flow changes from an orderly streamlined laminar flow to a disorderly turbulent flow. This occurs when the velocity field of the blood fluid is stochastic. Compared to laminar velocity profile, the turbulent flow velocity profile is much blunter at the central portion of the tube and much sharper at the walls. In addition, turbulent flow tends to form a number of eddies. Atherosclerotic lesions are often found at sites of turbulence in the arterial system because the mass transfer flux of atherogenic particles rely on turbulence eddies.

The criterion to distinguish a flow as turbulent or laminar is the dimensionless Reynolds number. The Reynolds number, Re, is $d \cdot u_0 / \nu$ where d is the diameter of the blood vessel, u_0 is the mean blood velocity, and ν is the kinematic viscosity of the fluid. Re is physically interpreted as the ratio between inertial and viscous forces. At low Re, blood flow is dominated by viscous forces which result in orderly laminar flow. When inertial forces dominate the flow, Re is high and the flow is turbulent. In general, blood flow is laminar at Re less than 2000. The critical Re is the transitional limit of the flow from laminar to turbulent. For transition to turbulence, blood flow through an artery generally has a critical Re of ~2300. In a bifurcation, however, critical Re is ~600 and can be as low as 400 for flows with high risk of turbulence [55].

The boundary layer is a crucial element of blood flow in the arteries because exchange of cells or blood constituents, e.g. LDL, between the blood and the arterial wall is dominated by convective and diffusive phenomena within the boundary layer. Boundary layer theory is based on the assumption that close to the vessel wall there exists a thin layer of fluid that is mostly governed by viscous forces and outside that layer, those viscous forces may be neglected. In the boundary layer, the velocity changes from zero at the wall to a velocity unimpeded by viscous forces. The boundary layer remains intact unless the angle of fluid motion along the wall surface is too large in which case the boundary layer may detach itself, creating vortices and wakes. Plasma flow in the boundary layer near the arterial wall is laminar.

Finally, viscous properties of blood can also affect its hemodynamic behavior. The viscosity of fluid is defined by $\mu = \tau / \dot{\gamma}$ where μ is the viscosity; τ is the shear stress and $\dot{\gamma}$ is the shear rate. A fluid is known as a Newtonian fluid when its viscosity at a specified temperature is constant. Plasma behaves generally as a Newtonian fluid. The whole blood, however, is non-Newtonian because of its aggregation properties at low shear rates, but it may be considered reasonably Newtonian for shear rates greater than 100 sec^{-1} and vessel diameter greater than 0.3 mm.

4.2. Heterogeneous Reaction

Heterogeneous reaction is an important physicochemical operation. The reaction takes place at certain phase boundaries and is greatly determined by hydrodynamic factors. This reaction consists of three stages. The first stage is the mass transfer flux of reaction particles in a solution to a reaction surface at the phase boundaries. The second stage is the heterogeneous reaction itself at the surface. The final stage is the reaction products that depart from the reaction surface. Our models will focus on the first process, the mass transfer flux stage, because both second and third stages are dependent on the first.

4.3. Mass Transfer Flux

The transport of blood solutes such as LDL from the blood to the arterial wall is a major contribution to atherosclerosis. The mass transport of these blood solutes is governed by several different mechanisms. The first of these mechanisms is the biomacromolecular diffusion of solutes induced by a concentration gradient. Consider a low solute concentration in human blood with a constant diffusion coefficient. The diffusive flux has the form

$$J_c = -D \nabla c \tag{4}$$

where D is the diffusion coefficient, ∇c is the gradient of the solute concentration distribution, and J_c is the diffusive flux in the direction of decreasing concentration. The second mechanism is the convection of the solute in which circulating LDL are transferred through the bloodstream. The convective flux has the form

$$J_u = c u_i \tag{5}$$

where u_i is the velocity vector of blood fluid. The third mechanism, natural convection, is caused only by the density gradient of the solute in a fluid layer near the reaction surface. The gradient is derived from the concentration change of LDL at the surface. The mass transfer flux of blood solutes, such as LDL, from the bloodstream to the arterial endothelium of lesion-prone sites is governed by these three mechanisms.

4.4. Thermodynamics Interface

Atherogenesis is related to nanoscale fluid dynamics and macromolecular transport at the arterial endothelium [29]. The behavior of atherosclerosis is time-dependent, and the dominant phenomena may occur in the range of 0-100 Å. Thus, information about the surface is very difficult to obtain. The adherence of an initial lesion on the arterial endothelium can be treated as a thermodynamics problem in a mixing system because thermodynamics deals with macroscopic and statistical behaviors of interface rather than with details of their molecular structures. The terms surface free energy, work of adhesion, surface stress, and contact angle are used in describing a plasma-endothelial interface in the thermodynamics model.

The surface free energy, γ, a major thermodynamics quantity used to characterize an interface, is the reversible work used to create a unit area of surface at constant temperature, volume, and chemical potential $i(\mu_i)$. The surface free energy γ of a newly created surface is the amount of surface work (dw) done to form the new surface area (dA) and is defined as

$$\gamma = \frac{dw}{dA} \tag{6}$$

In liquid, but not in solid, the surface free energy can be interpreted as the surface stress or tension, which is the work necessary to stretch or compress an existing surface.

When phase A adsorbs to phase B, there will be a surface energy of adhesion, E_{AB}, or also called the work of adhesion, W_{AB}, between the two different phases. The Helmholtz interfacial free energy (or tension), γ_{AB}, is defined as

$$\gamma_{AB} = \gamma_A + \gamma_B - W_{AB} \tag{7}$$

A newly formed surface may restructure with time and will reach some equilibrium with its surrounding environment.

According to Young's equation, the equilibrium of the interfacial tensions at a liquid-solid interface is expressed as

$$\gamma_S = \gamma_{SL} + \gamma_L \cos\theta \tag{8}$$

where θ is the equilibrium contact angle, γ_S is the solid surface free energy, γ_L is the liquid surface free energy and γ_{SL} is the surface free energy at the liquid-solid interface. Combining Eq. (7) and (8) results in the work of adhesion, W_{SL}, which is expressed using the contact angle

$$W_{SL} = \gamma_L(1+\cos\theta) \tag{9}$$

The contact angle technique is one of the most sensitive methods known for obtaining true surface information.

5. MATHEMATICAL MODELS

Since the blood flow is confined to a circulation system, the flow obeys the conservation principles of mass, momentum and energy. The entity balance and conservation principles are used to construct the mathematical models.

5.1. Continuity Equation

Consider the mass M of a blood density $\rho(x,t)$ in a volume V

$$M = \int_V \rho(x,t)\, dV \tag{10}$$

where $\rho(x,t)$ is a continuously differentiable function of spatial coordinates $x(x_1,x_2,x_3)$ and time t. Given that masses are neither created nor destroyed in a conservative system from Eq. (2), we impose the condition $DM/Dt = 0$ to yield the continuity equation of the blood fluid

$$\frac{\partial \rho}{\partial t} + \nabla\cdot(\rho u_i) = 0 \tag{11}$$

where $u_i(x,t)$ is the velocity vector with components (u_1,u_2,u_3) and ∇ is the gradient vector operator.

5.2. Equations of Motion

The conservation of momentum states that the rate of change of momentum of the body is equal to the force acting on the body, which is expressed by the following equation of motion

$$\rho\left[\frac{\partial u_i}{\partial t}+(u_i\cdot\nabla)u_i\right]=\nabla\cdot\sigma_{ij}+\rho F_i \tag{12}$$

where σ_{ij} is the stress tensor where $i,j=1,2,3$ and $F_i(x_i,t)$ denotes the body force vector per unit mass. The stress tensor of the fluid is $\sigma_{ij}=-p_iI_{ij}+d_{ij}$ where $-p_iI_{ij}$ is the isotropic stress tensor with unit tensor I_{ij} at a hydrostatic pressure p_i and d_{ij} is the non-isotropic stress tensor or the deviatoric stress tensor caused entirely by the fluid motion. The fluid is assumed to be isotropic and d_{ij} is assumed to be linearly dependent on the local velocity gradients. The fluid under these two assumptions is known as a Newtonian fluid with the following constitutive relation

$$d_{ij}=2\mu\left[e_{ij}-\frac{1}{3}(\nabla\cdot u_i)I_{ij}\right]\quad i,j=1,2,3 \tag{13}$$

where $e_{ij}=\frac{1}{2}\left[\frac{\partial u_i}{\partial x_j}+\frac{\partial u_j}{\partial x_i}\right]$ is the symmetric part of the velocity gradients tensor called the rate of strain tensor, and μ is the fluid viscosity.

Substitution of Eq. (13) into (12) yields the Navier-Stokes equation that governs the motion of fluid

$$\rho\left[\frac{\partial u_i}{\partial t}+(u_i\cdot\nabla)u_i\right]=\nabla\cdot\left[2\mu[e_{ij}-\frac{1}{3}(\nabla\cdot u_i)I_{ij}]\right]-\nabla p_i+\rho F_i \tag{14}$$

If we take the temperature to be uniform over the fluid, an isothermal fluid, then the Navier-Stokes equation reduces to

$$\rho\left[\frac{\partial u_i}{\partial t}+(u_i\cdot\nabla)u_i\right]=\mu\left[\nabla^2u_i+\frac{1}{3}\nabla(\nabla\cdot u_i)\right]-\nabla p_i+\rho F_i \tag{15}$$

where ∇^2 denotes the Laplace operator. For an incompressible, isothermal and Newtonian fluid, Eq (11) and (15) further reduces to

$$\nabla\cdot u_i=0 \tag{16}$$

$$\rho\left[\frac{\partial u_i}{\partial t}+(u_i\cdot\nabla)u_i\right]=\rho F_i-\nabla p_i+\mu\nabla^2u_i \tag{17}$$

where $\rho\frac{\partial u_i}{\partial t}$ is the transient acceleration term, $\rho(u_i \cdot \nabla)u_i$ is the convective acceleration term, ρF_i is the body force term, $-\nabla p_i$ is the pressure gradient term, and $\mu\nabla^2 u_i$ is the viscous force term.

For an axisymmetric flow in a tube, Eqs. (16) and (17) is expressed in cylindrical coordinates as

$$\frac{\partial u_r}{\partial r}+\frac{u_r}{r}+\frac{\partial u_z}{\partial z}=0 \tag{18}$$

$$\frac{\partial u_z}{\partial t}+u_r\frac{\partial u_z}{\partial r}+u_z\frac{\partial u_z}{\partial z}=F_z-\frac{1}{\rho}\frac{\partial p}{\partial z}+\frac{\mu}{\rho}\left(\frac{\partial^2 u_z}{\partial r^2}+\frac{1}{r}\frac{\partial u_z}{\partial r}+\frac{\partial^2 u_z}{\partial z^2}\right) \tag{19}$$

$$\frac{\partial u_r}{\partial t}+u_r\frac{\partial u_r}{\partial r}+u_z\frac{\partial u_r}{\partial z}=F_r-\frac{1}{\rho}\frac{\partial p}{\partial r}+\frac{\mu}{\rho}\left(\frac{\partial^2 u_r}{\partial r^2}+\frac{1}{r}\frac{\partial u_r}{\partial r}-\frac{u_r}{r^2}+\frac{\partial^2 u_r}{\partial z^2}\right) \tag{20}$$

where u_r is the radial velocity component and u_z is the axial velocity component.

5.3 Convective Diffusion Equation

Consider a conservative system of volume V that contains blood particles. A surface S bounds the volume. Following mass conservation and entity balance, the transport of particle mass without creating or destroying the quantities in the system can be expressed as

$$\int\frac{\partial c}{\partial t}dV=-\oint J\,dS \tag{21}$$

where $J=cu_i-D\nabla c$ is the sum of diffusive and convective flux from Eq. (4) and (5). The left side of Eq. (21) represents the rate of change of the number of particles in the volume and the right side is the number of particle that moves into the volume. Eq. (21) can be rewritten in the differential form as

$$\frac{\partial c}{\partial t}=-div(D\ grad\ c)-div(cu_i) \tag{22}$$

For an incompressible fluid with a constant diffusion coefficient D, Eq. (22) simplifies to the following convective diffusion equation

$$\frac{\partial c}{\partial t} + (u_i \cdot \nabla)c = D\nabla^2 c \tag{23}$$

Eq. (23) in Cartesian coordinates is

$$\frac{\partial c}{\partial t} + u\frac{\partial c}{\partial x} + v\frac{\partial c}{\partial y} + w\frac{\partial c}{\partial z} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right) \tag{24}$$

6. ANALYTICAL MODELS

6.1. Mass Transfer Flux (MTF) Model of Atherogenic Particles

Following the terms, concepts, and methods in the Physical Systems and Mathematical Models sections, we create a bioheterogeneous reaction model, a natural convection model and a boundary value model to investigate the mass transport flux of LDL and monocytes from the blood phase to the atherosclerotic lesion phase. The symbols used are denoted in the nomenclature at the end of the chapter.

Bioheterogeneous Reaction Model

Bioheterogeneous Reaction

The bioheterogeneous reaction of atherosclerosis occurs at a plasma-endothelial interface and is largely dependent on local hemodynamics. This reaction consists of three stages: The first stage is the mass transfer flux of LDL and monocytes in blood to a reaction surface of the arterial endothelium at the lesion-prone sites. The second stage is the bioheterogenous reactions between these transferred solutes and endothelial cells at the surface, which leads to LDL particles and monocyte cells being filtered onto the surface and accumulating in the subendothelium. The final stage is the promotion of atherogenesis by the reaction products at these sites. We will focus on the first mass transfer flux stage because both the second and third stages are dependent on the first.

Local Blood Flow

Clinical and experimental observations [63-67] show that atherogenesis is often found in regions of arterial bifurcations, branching or curvatures, where the bloodstream is characterized by disturbed non-axial flow, reverse flow, flow separation and stagnation. Following Sections 4.1 Hemodynamic Behaviors and 4.3 Mass Transfer Flux, the blood flow in regions of lesion-prone sites may be nominally divided into three zones. The first zone is the disturbed flow region farthest from the reaction surface. In this zone, both solute concentration and density are constant because blood constituents and momentum are transferred by eddies. The second zone, nearer to the surface, is called the momentum boundary layer where the plasma laminar flow by molecular viscosity occurs. In the boundary layer, there are solute concentration changes and density gradients caused by the solute concentration change at the surface. Since kinematic viscosity of fluid is larger than its diffusion coefficient, the momentum and solute in the layer are mainly transferred by eddies

that rapidly decay toward the surface. Finally, the third zone, called the diffusion boundary layer, is nearest to the reaction surface where eddies are negligible, and LDL or monocytes are transferred by diffusion. The fluid motion in the layer is governed by natural convection.

Consider blood flow through a branched vertical artery tube of internal radius a, where (r,θ,z) is a set of cylindrical coordinates with the z-axis coinciding with the axis of the tube. The flow at the border between the momentum boundary layer and the disturbed flow zone has to satisfy the following continuity condition:

$$u_r = V_d \text{ at } r = a - h \tag{25}$$

where u_r is the radial velocity component of plasma fluid in the momentum boundary layer, V_d is the eddy in the disturbed region and h is the thickness of the momentum boundary layer. Effects of local hemodynamic factors on the bioheterogeneous reaction are determined by the interactions of blood flow among the three mentioned zones.

Natural Convection Model

Governing Equation

Using same notations, we investigate the plasma flow over a reaction surface in the momentum boundary layer in the range of $(a-h) \le r \le a$, $0 \le \theta \le 2\pi$, $-\infty < z < \infty$ and under body forces because atherosclerotic lesion arises from the layer. Denote the concentration of solute far from the surface as c_0 and at the surface as c_1. As indicated in the second stage of the bioheterogenous reaction (Section 4.2), a decrease in c_1 corresponds to LDL or monocytes being filtered into the subendothelium. If the concentration difference $(c_0 - c_1)$ is sufficiently high, natural convection in a fluid layer near the surface will be generated with a velocity component u_z in the axial direction of the tube, which will vary with the radius r. The natural convection model corresponds to a physical situation of atherosclerotic event at the location. Since plasma fluid is known to be Newtonian, we will use the set of differential equations (11), (17) and (23) outlined in the Mathematical Models section to investigate the physical situation at the momentum boundary layer,

Assumptions

Based on the Physical System section, the following assumptions are used to simplify Eqs (11), (17), and (23):

(1) The plasma is an isothermal and incompressible fluid.
(2) The rate of plasma flow is steady.
(3) The pressure gradient in the momentum boundary layer is negligible because the pressure field in the disturbed flow zone is constant.
(4) The solute concentration is low and the rate of concentration change is steady.
(5) The diffusion coefficient is considered constant due to low solute concentration.
(6) The viscous dissipation in the fluid is negligible.

(7) Edge effects become negligible since the length of the tube is long compared to the region being studied.
(8) The flow does not slip on the endothelial surface of the arterial vessel.
(9) The diameter of the tube does not vary with internal pressure.

These assumptions are used in most studies of hemodynamics and mass transport [13,54,58,60,61].

Simplified Governing Equation

Because the momentum boundary layer overlaps the diffusion boundary layer in the model, we analyze the plasma flow under body forces in the momentum boundary layer. Since $a >> h$, the flow is considered planar in a vertical semi-infinite plane at $0 \le y \le h$ and $-\infty < x < \infty$, where x-axis is along the plane surface and toward the flow direction, and y-axis is outward normal of the surface. Using Boussinesq's approximation that neglected density variations with concentration in all terms except for the body force, Eqs. (11), (17), and (23) in Cartesian coordinates are simplified to:

$$\frac{\partial u_y}{\partial y} + \frac{\partial u_x}{\partial x} = 0 \tag{26}$$

$$u_y \frac{\partial u_x}{\partial y} + u_x \frac{\partial u_x}{\partial x} = \frac{F_x}{\rho} + \nu \frac{\partial^2 u_x}{\partial y^2} \tag{27}$$

$$u_y \frac{\partial c}{\partial y} + u_x \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial y^2} \tag{28}$$

where u_x and u_y are the velocity components of fluid in the x and y directions respectively, F_x is the body force component consisting of the transient inertial force and gravitation in the x direction and $\nu = \mu / \rho$ is the kinematic viscosity of plasma. Eqs. (27) and (28) have been simplified by taking into account $\frac{\partial^2 u_x}{\partial y^2} >> \frac{\partial^2 u_x}{\partial x^2}$ and $\frac{\partial^2 c}{\partial y^2} >> \frac{\partial^2 c}{\partial x^2}$.

Boundary Conditions

According to the previous models and assumptions, the boundary conditions of the boundary value model are:

$$u_x = 0,\ u_y = 0,\ c = 0 \text{ at } y = 0 \tag{29}$$

$$u_y = V_d \text{ at } y = h \tag{30}$$

$$c = c_o \text{ at } y \to \infty \tag{31}$$

Mass Transfer Flux

Applying conditions (29)-(31) to Eqs. (26)-(28) yields the following concentration distribution of blood solute in the diffusion boundary layer

$$c = 0.69\, c_0 y \left(\frac{{v_d}^3}{D^{11}\nu^4}\right)^{\frac{1}{27}} \left(\frac{(g\cos\alpha + \omega u_0)k}{x}\right)^{\frac{2}{9}} \tag{32}$$

Substituting Eq. (32) into (4) yields the mass transfer flux of the solute to the reaction surface:

$$J = 0.69\, c_0 \left(\frac{{v_d}^3 D^{16}}{\nu^4}\right)^{\frac{1}{27}} \left(\frac{(g\cos\alpha + \omega u_0)k}{x}\right)^{\frac{2}{9}} \tag{33}$$

with J being the flux toward the inner artery wall, g being the gravitational acceleration, atherosclerotic parameters c_o being the LDL or monocyte concentration in human blood, ω being the heart rate, u_0 being the transient mean velocity of blood fluid in the axial direction of the arterial vessel near the studied region, v_d being eddies determined by local dynamics of the fluid, ν being the kinematic viscosity of plasma fluid in the region, x being the diffusional length of LDL or monocyte along the inner artery wall, D being the diffusion coefficient of atherogenic particles, k being the density parameter determined by concentration change and α being the angle between the mean velocity and gravity. We will refer to Eq. (33) as the atherosclerotic mass transfer flux equation or AFE for short.

6.2. Analytical Results and Clinical Implications of MTF Model

The MTF model provides a means to analytically study the relationship among atherogenic factors including blood LDL or monocyte concentration, heart rate, transient mean blood velocity, eddy velocity, kinematic viscosity, diffusional length and diffusion coefficient of atherogenic particles, the density parameter, and the angle between the mean velocity and gravity. These factors are combined through Eq. (33), the atherosclerotic mass transfer flux equation (AFE), which describes the total flux of atherogenic particles to the lesion prone sites where an atherogenic event can occur.

Assessing Lipid-Lowering Therapy

From the AFE, a 1% reduction in LDL concentration results in a 1.2% reduction in the disease risk. Epidemiological studies have shown that a 1% reduction in an individual's total plasma LDL level lead to a 1.5 to 2.0 % reduction in the risk [68,69]. The clinical studies are in good agreement with results of the MTF model and indicate that the model can provide a

reliable theoretical baseline for lipid-lowering therapy. By determining the lipid concentration change due to therapy, we study the impact of the concentration change on mass transfer flux of LDL using AFE and quantitatively assess therapeutic efficacy of the treatment. Epidemiological results that show greater reduction in risk than our predicted results may indicate additional protection from disease by the therapy.

Non-independent Contribution of Risk Factors

While the relative impact of risk factors is determined by the individual's physiological parameters, the contribution of risk factors to the disease may vary greatly among individuals as predicted by the AFE. For example, autopsy and clinical studies [13-14,16,22] suggested that regions of arterial bifurcations, branching or curvatures had the greatest predilection for atherosclerosis. Internal angles among 70 human aortic bifurcations can vary widely from 10 to 70 degrees [70]. Different internal angles in physiologically different bifurcations amongst people may lead to different α in the AFE. Thus internal angle may be a greater risk factor under some conditions. To illustrate, take two different internal angles 15° and 45°. Under a 1% increase in individual's LDL level, AFE produces a 7.2% higher risk for 15° than for 45°. This 7.2% risk caused by the difference in bifurcation angle is significantly higher than the 1.2% increase in risk from 1% increase in LDL level alone as mentioned previously. The case shows that arterial geometry in certain instances can play a greater role in atherosclerosis than simply LDL level alone. Therefore, AFE not only can give relative impact of various risk factors, but can also show how certain risk factors can dominate others depending on the person's physiological parameters. Simply put, the contribution of risk factors is conditionally dependent on the person's physiology. There is not a simple independent relationship between physiological parameters and the risk of disease, but rather the risk of disease is a combination of the physiological parameters themselves and their impact on one another. This observation may explain the sometimes inconsistent results that are produced from just using independent risk factors to explain the cause of atherosclerosis [72]. The MTF model is therefore useful in determine the interaction among the atherogenic parameters and their overall impact on risk of disease.

Optimizing Therapeutic Treatment

Epidemiological studies suggest that elevated LDL level in blood, inflammation, infectious agents, smoking cigarette and depression are risk factors [20,31,32]. Both experimental and clinical evidences indicate that increased heart rate is also associated with atherosclerosis [49,50]. However, it is difficult to assess the combined contribution of these factors to the disease. The MTF model can be used to quantitatively assess the risk factors and generate an efficient sequence of therapy for the treatment of the disease.

For example, AFE predicts a 0.2% increase in the risk of disease from a 1% increase in heart rate, which may be induced by smoking or stress. A 1% increase in leukocyte-monocyte concentration in the blood, which may be cause by infectious agents, results in a 1.2% increase in the risk of disease. A 1.0% increase in both the individual's monocyte level and heart rate leads to a 1.4% increase in the total risk. We therefore conclude that the infectious agent is our first therapeutic target and smoking is the second target. This example illustrates that AFE can be a potential method to optimize therapeutic treatment that ranks the contributions of various risk factors to atherosclerosis.

6.3. Lesion Adherence Model

Following the terms, concepts, and methods in the Physical Systems and Mathematical Relations sections, we will create a thermodynamics model and a boundary value model to explore mechanisms of atherosclerosis, in particular the initial stage of lesion adhesion, and to explain clinical results.

Thermodynamics Model

Thermodynamics Model of Atherosclerotic Lesion

The arterial endothelium is always in direct contact with the blood flow and is borne by hemodynamic forces. Endothelial cells have synthetic and metabolic capabilities and act as selectively permeable barriers for the transportation of macromolecules. The interfacial forces acting on the endothelium can change endothelial functions and structures including increased molecular permeability, LDL accumulation, and endothelial cell damage. In this model, an initial lesion adhered on the endothelium is investigated using thermodynamics and energy conservation principles.

Let us consider the blood flow through a branched circular arterial tube of internal radius a under an axial transient inertial force f, where (r,θ,z) is a set of cylindrical polar coordinates with the z-axis coinciding with the axis of the tube. Taking a small fluid element near the inner tube wall at a branch point where $r = a$ and $z = 0$, the kinetic energy of the element E_k is $\frac{1}{2}\cdot\rho\cdot V\cdot u_l^{\,2}$, where ρ is the density of the fluid, V is the volume of the element, and u_l is the velocity vector of the element. If an initial lesion occupies the element, E_k becomes the kinetic energy of the lesion. This lesion is characterized by volume V, axial adhesive length of the lesion on the endothelium L_a, contact area between the lesion and the endothelium A, surface free energy γ_{sl}, velocity vector u_l, and interfacial shear resistance F_a, which is the force resisting the movement of the lesion (Fig. 2).

Energy Equations

The adherence of an initial lesion on a plasma-endothelial interface can be treated as a thermodynamics problem in a mixing system because thermodynamics deals with macroscopic and statistical behaviors of interfaces rather than with details of their molecular structures. Surface energy of adhesion E_{sl} is the energy that is required to bring LDL from the interior of the blood fluid into the arterial endothelium and form an interface. Consider a lesion under an axial transient inertial force f (Fig. 2).

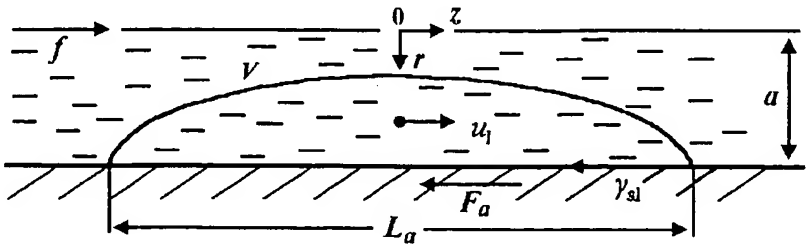

Figure 2. Axial cross-section of a lesion adhered on the arterial endothelium.

Based on thermodynamics and energy conservation principles, the energy equations for the lesion are created as

$$E_k = \frac{1}{2} \cdot F_a \cdot L_a \cdot A \tag{34}$$

$$E_{sl} = \frac{1}{2} \cdot F_a \cdot L_a \tag{35}$$

$$E_k = E_{sl} \cdot A \tag{36}$$

where $E_{sl} = \gamma_s + \gamma_l - \gamma_{sl}$ according to the Eq. (7) of the Thermodynamics Interface section.

Eq. (34) describes the equivalence between the kinetic energy of a lesion E_k and the work done by the total interfacial shear resistance $F_a \cdot A$ along the adhesive length L_a. Eq. (35) represents the equivalence between the surface energy of adhesion E_{sl} and the work done by F_a at a plasma-endothelial interface. Substitution of Eq. (35) into Eq. (34) yields Eq. (36). If E_k is greater than $E_{sl} \cdot A$, then the lesion will not form because the kinetic energy of the lesion E_k overcomes the total energy of adherence $E_{sl} \cdot A$ before the adherence of the lesion can occur.

Dynamic Boundary Value Model

Governing Equations

Studies of hemodynamics [6,8,13,21,63-67] suggest that atherosclerotic lesions are located in regions of reduced shear stress of the fluid, which is often associated with flow separation and turbulence. A transient boundary layer, led by turbulent flow, occurs in these regions. The studies also indicated that blood flow near inner arterial walls consists mainly of plasma fluids.

In the dynamic model, the plasma viscous flow in the transient boundary layer near the inner tube wall at lesion-prone sites is investigated because lesions arise in this layer. The plasma flow through a circular tube is governed by Eq. (17).

Assumptions

According the terms and concepts in the Physical Systems section, the following assumptions are imposed to simplify the boundary value model:

(1) The gravitational potential in the fluid has a negligible effect because the transient boundary layer is thin.
(2) The rate of flow is steady, and there is a constant pressure flow.
(3) The flow does not slip at the inner wall of the tube.
(4) The length of the tube is long compared to the region being studied, so that edge effects become negligible.
(5) The diameter of the tube does not vary with internal pressure.
(6) The convection in the flow may be negligible in the model.

These assumptions are valid in most studies of hemodynamics [13,54,58,61].

Simplified Governing Equations

Let us use the same notations and consider an incompressible plasma flow in a circular arterial tube with ranges $(a-h(z)) \le r \le a$, $0 \le \theta \le 2\pi$, and $-\infty < z < \infty$, where $h(z)$ is the thickness of the transient boundary layer. Following the above assumptions and using cylindrical coordinates (r,θ,z), Eq. (17) is simplified to

$$f = \frac{1}{r} \cdot \frac{d}{dr}(\tau_{rz} \cdot r) \tag{37}$$

and

$$\tau_{rz} = -\mu \cdot \frac{du_z}{dr} \tag{38}$$

where u_z is the axial velocity component of the plasma fluid, τ_{rz} is the axial viscous shear stress of the fluid, f is the axial transient inertial force, and μ is the viscosity of plasma.

Boundary Conditions

According to previous assumptions, the boundary conditions of the model are

$$u_z = 0 \text{ at } r = a \tag{39}$$

$$\tau_{rz} = F(z) \text{ at } r = a \tag{40}$$

where $F(z)$ is the shear force acting on the inner wall of the tube.

If a fatty streak occurs at $r = a$ and $z = 0$, we can substitute $F(z) = F_a$ into Eq. (40) to yield

$$\tau_{rz} = F_a \text{ at } r = a,\ z = 0 \tag{41}$$

where the interfacial shear resistance F_a is defined in the previous model. Through Eq. (41), we can now join the thermodynamic model to the boundary value model.

Compatibility Condition

As stated previously, there is often turbulent flow at the location of atherosclerosis. The flow at these sites consists of two different types. The first is the plasma flow in the transient boundary layer that is governed mainly by the viscous force. The second is the blood flow in the rest of the regions of the tube that is governed by the axial transient inertial force. Hence, the viscous force and the transient inertial force must equal at the border of the layer for a unique analysis solution. The compatibility condition is created as

$$\tau_{rz} = f_h \text{ at } r = a - h(z) \tag{42}$$

where f_h is the axial transient inertial force per unit area. We may take $f_h = f \cdot (a - h(z))$.

Analytical Solutions

Eq. (37) and Eq. (38) combined with Eq. (39), (40), and (42) yield the following axial shear stress of the plasma fluid τ_{rz}, axial velocity component u_z, and compatibility equation:

$$F(z) = f \cdot \left(a - h(z) + \frac{h(z)^2}{2a} \right) \tag{43}$$

$$u_z = \frac{f}{4\mu} \cdot (a^2 - r^2) + \frac{f}{2\mu} \cdot (a - h(z))^2 \cdot \ln\left(\frac{a}{r}\right) \tag{44}$$

$$\tau_{rz} = \frac{f}{2r} \cdot (a - h(z))^2 + \frac{r \cdot f}{2} \tag{45}$$

Substitution of $F(z) = F_a$ into Eq. (43) yields

$$F_a = f \cdot \left(a - h(z) + \frac{h(z)^2}{2a} \right) \tag{46}$$

Substitution of Eq. (35) into Eq. (46) yields

$$E_{sl} = \frac{1}{2} \cdot L_a \cdot f \cdot \left(a - h(z) + \frac{h(z)^2}{2a} \right) \tag{47}$$

We will refer to Eq. (47) as the adhesion energy equation (AEE).

Effect of Eddies on Atherosclerosis

Turbulence eddies do not originate in the transient boundary layer, but these eddies may enter the layer from the side $r < (a - h(z))$. If we consider the effect of the eddies in the layer on atherosclerosis, the thickness of the layer $h(z)$ in the region of the lesion-prone sites can be expressed approximately as $h(z) \approx B \cdot v_d$ (48)

where eddy velocity v_d is a weak function of z and varies with r. Parameter B is determined by the axial velocity u_b of the plasma fluid at the border of the layer and the axial distance z_h between the point being studied and the starting point in the layer.

The transport of LDL and monocytes in blood to a plasma-endothelium interface at the lesion-prone sites may be closely related to v_d. Eq. (48) indicates that increased $h(z)$ involves increased v_d, which implies that LDL in the plasma fluid are more likely to be drawn into the endothelium. Increased thickness of the transient boundary layer $h(z)$ and increased eddy velocity v_d in regions of the lesion-prone sites are risk factors in atherogenesis.

6.4. Analytical Results of Lesion Adherence Model

Using Eq. (47), the adhesion energy equation (AEE), we can obtain representative results using some typical values for a human abdominal aortic vessel [58]. Take the mean internal radius of the vessel to be $a = 0.5\ cm$, mean transient axial velocity to be $u_0 = 15\ cm \cdot s^{-1}$, mean transient frequency to be $\omega = 2\ s^{-1}$, density to be $\rho = 1.0\ g \cdot cm^{-3}$, adhesive length to be $L_a = 0.2\ cm$, and the range of the thickness of the transient boundary layer $0 \le h(z) \le 0.1\ cm$. Since $f = \rho \cdot \omega \cdot u_0$, we get the axial transient inertial force $f = 30\ g \cdot cm^{-2} s^{-2}$.

To analyze the dynamic boundary value model, substitute $r = 0.4\ cm$ and the above mentioned values into Eq. (45) to produce a relationship between the shear stress of the

plasma fluid and the thickness of the transient boundary layer (Fig. 3). For the thermodynamics model, substitution of the above mentioned values into the AEE (Eq. 47) produces a relationship between the surface energy of adhesion and the transient boundary layer (Fig. 4).

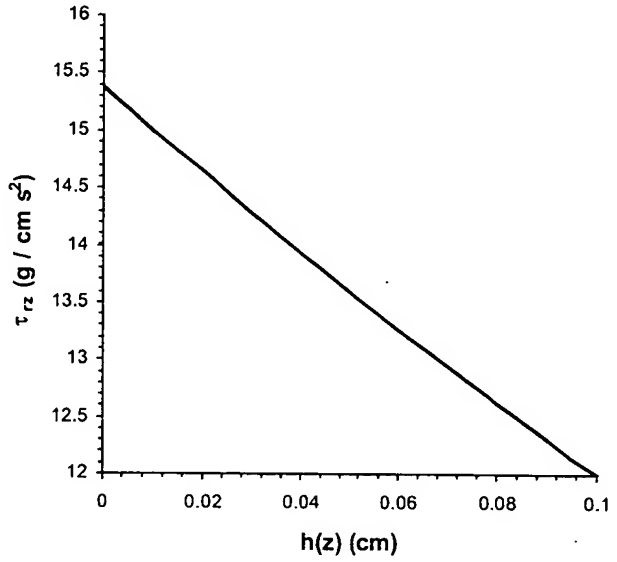

Figure 3. The relationship between the shear stress of the plasma fluid and the thickness of the transient boundary layer.

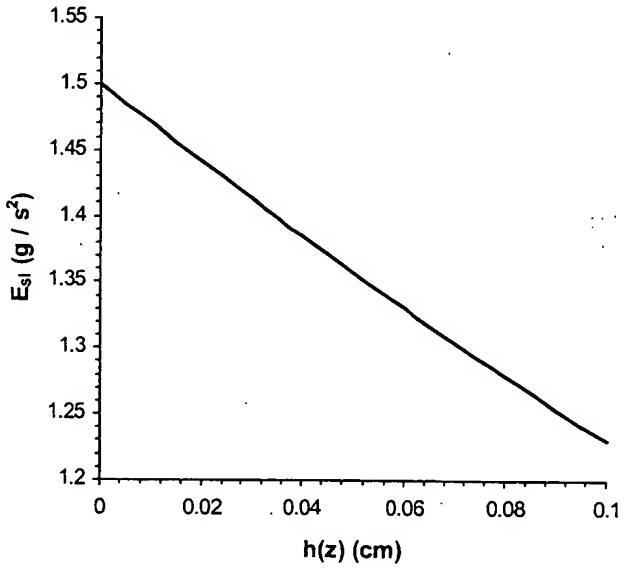

Figure 4. The relationship between the surface energy of adhesion and the thickness of the transient boundary layer.

8. CONCLUSIONS

We have demonstrated how analytical techniques can be used to investigate atherogenic events such as the transfer of LDL particles from the bloodstream to the endothelial wall and the thermodynamics mechanism of how the LDL particles adhere to the wall. The following conclusions are drawn from the specifics of the two models.

8.1. Mass Transfer Flux (MTF) Model of Atherogenic Particles

We propose that the variables in the AFE be considered as atherosclerotic parameters. The mass transfer flux determined by the AFE can be used to determine the causes of atherosclerosis and their relative contributions and relationship to the risk of disease. The AFE has therefore united some crucial factors from main theories of atherosclerosis and integrated risk factors [14,20,31,32,37] into a single analytical parameter, the mass transfer flux, in order to evaluate their contribution.

The analytical MTF model can explain some of the following clinical and experimental observations.

(1) Lipid-lowering therapy plays a central role in clinical prevention and treatment of atherosclerosis. Our model shows that LDL concentration should be indeed first considered clinically because the LDL parameter c_o has the largest impact on the AFE. We believe that increased LDL and monocytes levels in blood are a primary risk factor because it directly leads to an increase in mass transfer flux and thus accumulation of the substance within the subendothelium.

(2) Not any single one, but a combination of the proposed parameters should be considered when devising preventive and therapeutic actions against atherosclerosis. Relative impact of the parameters to the treatment can be evaluated using the mass transfer flux of the AFE. The flux may therefore be used as a theoretical baseline for efficacy of therapeutic intervention and possible regression of the disease.

(3) No endothelial defects seem to occur during formation of early lesions. This is because the plasma viscosity is lower at the lesion formation area than at its neighboring sites. According to our MTF model, the mass transport of blood solutes to the inner artery wall increases with a decrease in plasma viscosity, which also corresponds to a lower wall shear stress at atherogenic sites. Thus lesions tend to form near regions of low wall shear stress and high mass transfer flux.

(4) The mass transport of blood constituents exists not only in the diffusion layer but also in the momentum boundary layer and disturbed flow region such as at arterial branches or bends of lesion-prone sites.

The conclusions and analytic results of the MTF model are supported by major clinical and experimental evidences [8,13-15,20-21,31-32,36-37,46-50,68-69].

8.2. Lesion Adhesion Model

We obtain the following conclusions based on the Lesion Adhesion Model and our analytical solutions.

(1) From Eq. (45), Figs. (3) and (4), we find that the shear stress of the plasma fluid τ_{rz} is proportional to the surface energy of adhesion E_{sl} and inversely proportional to the thickness of the transient boundary layer $h(z)$. This means that reduced τ_{rz} results in increased $h(z)$ and reduced E_{sl}.

(2) Fig. 4 and Eq. (48) indicate that increased $h(z)$ involves reduced E_{sl} and increased eddy velocity v_d. Increased $h(z)$ in regions of lesion-prone sites is a dominant factor in the formation of initial lesions because, based on both of the previous models, reduced E_{sl} and increased v_d lead to atherosclerosis more easily.

(3) Clinical and experimental results [8,21,65] suggest that atherosclerosis occurs in regions of reduced τ_{rz}. According to *Conclusion 1* and Eq. (48), reduced τ_{rz} involves reduced E_{sl} and increased v_d. This suggests that LDL in the fluid is more prone to be drawn to the plasma-endothelial interface and initial lesions form more easily in regions of reduced τ_{rz}.

(4) Clinical and experimental results [6,8,13,21,63-67] show that locations of atherosclerosis are associated with flow separation and turbulence. Based on *Conclusion 1* and Eq. (48), lesion formation occurs at these locations because it is stimulated by increased $h(z)$ and v_d.

(5) Clinical results [8,13,19,21] show that no endothelial defects occur during the formation of initial lesions. According to *Conclusion 1* and Eq. (35), reduced τ_{rz} involves reduced interfacial shear resistance F_a, and since endothelial defects are closely dependent on F_a, lower value of F_a in the lesion formation area than those of its neighboring sites is therefore not the cause of endothelial defects initially.

(6) Clinical results [1,5,13,16,19,20] show that an initial lesion is caused by depositions of LDL on the arterial endothelium. According to the thermodynamics model and Eq. (36), LDL rather than HDL are drawn from the interior of the plasma fluid into the plasma-endothelial interface because the lower density of LDL yield a lower E_{sl} than the E_{sl} for HDL deposition. Therefore, reduced E_{sl} or less energy required for LDL deposition leads to atherogenesis.

(7) Clinical results [5,13,16,19,29,58] show that initial lesions do not form in veins and capillary vessels even though there is a lower τ_{rz} in veins than there is in arteries. This phenomenon can be explained by the lack of a transient boundary layer in veins and capillary vessels.

The above conclusions suggest that the locations of atherosclerotic lesions are associated with regions of increased transient boundary layer $h(z)$ and reduced surface energy of adhesion E_{sl}, which lead to atherogenesis in only a small region of the vast systems of blood vessels. Analytical results of the thermodynamics and boundary value model suggest that increased eddy velocity v_d and reduced E_{sl} in these regions of the arterial branch points are the main causes for the formation of initial lesions.

More specifically, increased $h(z)$ in regions of the arterial branch point is responsible for increased v_d and reduced viscous shear stress τ_{rz}. Reduced E_{sl} and increased v_d contribute to bring LDL from the interior of the plasma fluid to the plasma-endothelial interface, which lead to the formation of an initial lesion. LDL then passes through the arterial endothelium, accumulates in the subendothelium, and stimulates monocytes to enter this area. The monocytes may then engulf cholesterol, and the lesion progresses to a more advanced stage.

9. MECHANISM OF ATHEROSCLEROSIS

Fung [58] suggested that the most intriguing feature of atherosclerosis is its appearance only at certain arterial sites such as bifurcations, branching, and curvatures. It is known that many factors influence atherogenesis including dieting, environment, elevated level of LDL, inflammation such as rheumatoid arthritis, infectious agents such as Chlamydia pneumonia, hypertension, cigarette smoking, family history, genetics, depression, diabetes and obesity [20,31,32]. However, these factors affect not only these special sites but also the entire body. Out of the vast bodies of vessels in the human circulatory system, only a small segment will become atherogenic. What is the mechanism behind the deposition of LDL particles and monocytes cells onto these arterial walls and not others? The analytic methods discussed in this chapter can help explain the mysterious nature of the extreme localization of the disease. Atherogenesis appears only at these locations because the mass transfer flux of atherogenic particles and eddies in the blood always occur at these sites. There are no lesions in human veins and capillaries because the flux and eddies does not exist in theses vessels. Eq. (33) in the MTF model shows that the flux is dependent on the eddy parameter. A number of experimental studies indicated that the eddies occurred often at these special locations [13,22,63-67], confirming the above analytical results.

10. REMARKS

The analytical methods discussed in this chapter tackles atherosclerosis as a multifactor disease with differently combined risk factors dominating at different stages of disease in different individuals. The methods approached atherosclerosis as a mass transport process from the blood phase to the lesion phase and is supported by clinical and experimental evidences [1,5,13,16,19,32,36-37,47].

The analytic methods are sound because they are derived from the entity balance and conservation laws of mass and momentum, which govern the atherogenic process. The results

given by the analytical methods not only impact the understanding of atherosclero mechanism but also can be used in clinical practices. These results may allows physician t predict a total risk of the disease, to determine the primary cause of disease, to assess the therapeutic efficacy of treatment, and to optimize the treatment for the individuals who require diagnosis, prevention, and treatment of atherosclerosis. Analytical methods may play a crucial role when studying environmental influences, dieting, lifestyle, high blood pressure, exercise and genetic impacts on atherosclerosis when the reward of prevention and the potential for regression is maximal.

NOMENCLATURE

α	angle between mean velocity and gravity (degrees)
L_a	axial adhesive length (cm)
z_h	axial distance between point being studied and starting point of transient boundary layer (cm)
u_0	axial mean velocity of fluid (cm/s)
f	axial transient inertial force $(g/cm^2 \cdot s^2)$
f_h	axial transient inertial force per unit area at border of transient boundary layer $(g/cm \cdot s^2)$
u_z	axial velocity component of fluid (cm/s)
u_b	axial velocity of plasma fluid at border of transient boundary layer (cm/s)
F_i, F_e	body force vector $(g/cm^2 \cdot s^2)$
c, c_o, c_1	concentration of solute (mg/cm^3)
A	contact area between lesion and endothelium (cm^2)
ρ	density of fluid (g/cm^3)
D	diffusion coefficient of solute (cm^2/s)
x	diffusional length of solute (cm)
v_d	eddy velocity (cm/s)
g	gravitational acceleration (cm/s^2)
ω	heart rate (s^{-1})
a	inner radius of tube (cm)
F_a	interfacial shear resistance $(g/cm \cdot s^2)$
ν	kinematic viscosity of fluid (cm^2/s)
E_k	kinetic energy of lesion $(g \cdot cm^2/s^2)$
J, J_u, J_c	mass transfer flux of solute $(mg/cm^2 s)$

p	pressure vector $(g/cm \cdot s^2)$
u_r	radial velocity component of fluid (cm/s)
$F(z)$	shear force acting arterial wall $(g/cm \cdot s^2)$
τ_{rz}, τ	shear stress of fluid $(g/cm \cdot s^2)$
E_{sl}	surface energy of adhesion (g/s^2)
γ_l	surface free energy of liquid (g/s^2)
γ_{sl}	surface free energy of liquid-solid interface (g/s^2)
γ_s	surface free energy of solid (g/s^2)
$h(z)$	thickness of transient momentum boundary layer (cm)
u_x, u_y	velocity components in Cartesian coordinates (cm/s)
u_i	velocity vector (cm/s)
u_l	velocity vector of lesion (cm/s)
μ	viscosity of fluid $(g/s \cdot cm)$
V	volume of lesion (cm^3)

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ATHEROSCLEROSIS

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Review article

Analytical models of atherosclerosis

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Abstract

Atherosclerosis is responsible for ≈50% of all mortalities in the USA, Europe, and Japan. An innovative approach for investigating atherosclerotic lesions using a thermodynamic model and a boundary value model and an analytical example of a human abdominal aorta vessel with an initial lesion are presented in the paper. Analytical results given by both models propose that increased transient boundary layer thickness and reduced surface energy of adhesion in regions of the arterial branch points play crucial roles in initial lesion formation. This study also improves the understanding of atherosclerotic mechanisms and helps to interpret clinical and experimental results.

Keywords: Atherosclerosis; Analytical model; Thermodynamics; Surface energy of adhesion; Hemodynamics; Turbulence; Transient boundary layer; Atherosclerotic mechanism

Nomenclature

L_a axial adhesive length (cm)
z_h axial distance between point being studied and starting point of transient boundary layer (cm)
τ_{rz} axial shear stress of plasma fluid (g/cm s^2)
f axial transient inertial force (g/cm^2 s^2)
f_h axial transient inertial force per unit area at border of transient boundary layer (g/cm s^2)
u_z axial velocity of plasma fluid (cm/s)
u_b axial velocity of plasma fluid at border of transient boundary layer (cm/s)
F_e body force vector (g/cm^2 s^2)
A contact area between lesion and endothelium (cm^2)
ρ density of liquid (g/cm^3)
v_e eddy velocity (cm/s)
a inner radius of tube (cm)
F_a interfacial shear resistance (g/cm s^2)
E_k kinetic energy of lesion (g cm^2/s^2)
ω mean transient frequency (Hz)
$\bar{u}$ mean velocity of blood flow in abdominal aorta (cm/s)
P pressure vector (g/cm s^2)
$F(z)$ shear force (g/cm s^2)

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E_{sl} surface energy of adhesion (g/s^2)
γ_l surface free energy of liquid (g/s^2)
γ_{sl} surface free energy of liquid–solid interface (g/s^2)
γ_s surface free energy of solid (g/s^2)
$h(z)$ thickness of transient boundary layer (cm)
u velocity vector of fluid (cm/s)
u_l velocity vector of lesion (cm/s)
μ viscosity of liquid (g/s cm)
V volume of lesion (cm^3)

1. Introduction

Atherosclerosis is characterized by the thickening, hardening, and loss of elasticity of the inner arterial walls. These changes in the walls can lead to the obstruction of coronary bloodstreams. The earliest atherosclerotic lesions, called fatty streaks, are simple deposits of low-density lipoproteins (LDL) on the aortic endothelium. These streaks occur at a universal age of ten, but progress to more advanced stages at different rates in different people. In the second stage, the lesions are called fibrous plaques because they contain not only more smooth muscle cells, but also more collagens and elastic tissues. The final stage is the complex lesions that are of thrombus formation with deposits of fibrins and platelets. The American Heart Association (AHA) committee has defined a new classification of the human atherosclerotic phases from the fatty streaks to the complex lesions [1].

Since atherosclerosis is a major cause of mortality and morbidity in the world, a huge volume of research has been focused on the disease [1–18]. These research have been concerned mainly with dieting, environment, genetics, and immunity. A number of studies also attempted to identify the components and characteristics of lesions at various stages. Ross [2] contributed his response-to-injury hypothesis to the understanding of cellular and molecular mechanisms of atherosclerosis. These investigations indicated that hemodynamics might be closely related to atherosclerosis.

Atherogenesis is related to nanoscale fluid dynamics and macromolecular transport at the arterial endothelium [3]. The behavior of atherosclerosis is time-dependent and the dominant phenomena may occur in the range of 0–100 Å from the endothelium. The location of atherosclerosis is also associated with flow separation and turbulence. These factors cause the study of the effects of hemodynamics on atherosclerosis to be rather complex. Early works on these effects focused on endothelial transportation using excised tissue. Fry [19,20] initiated studies on the effect of increased shear stress on the endothelium and showed that endothelial cells remodel their shapes when the direction of flow is changed. Caro et al. [21,22] found that lesions occur in areas experiencing low and fluctuating wall shear stress. Recent reports discussed the progress in the studies of the effects of hemodynamics on atherosclerosis [23–29].

Fung [28] summarized these hemodynamic effects and pointed out that the most intriguing feature of atherosclerosis is its appearance only at certain arterial branch points. It is known that many factors influence atherogenesis including dieting, environment, diabetes, high blood pressure, genetics, and exercise. These factors, however, affect not only the special branch locations, but also the entire body. Then why will only a few feet, in miles of blood vessels in the human body, be destined to have atherosclerosis? Why do only LDL deposit on some arterial walls and not others? What is so unique about these locations? Throughout the history of the study of atherosclerosis, many researchers have been focusing on the understanding of these fundamental natures of atherosclerosis. This paper proposes some answers to these fundamental questions.

An innovative approach for investigating atherogenesis is developed using a thermodynamic model and a boundary value model. Conclusions given by this study propose two new factors in atherogenesis: increased transient boundary layer thickness and reduced surface energy of adhesion in regions of arterial branch points, which play crucial roles in atherogenesis.

2. Thermodynamic model

2.1. Thermodynamic model of an atherosclerotic lesion

The arterial endothelium is always in direct contact with the blood flow and is borne by hemodynamic forces. Endothelial cells have synthetic and metabolic capabilities and act as selectively permeable barriers for the transportation of macromolecules. The interfacial forces acting on the endothelium can change endothelial functions and structures including increased molecular permeability, LDL accumulation, and endothelial

cell damage. In this model, an initial lesion adhered on the endothelium is investigated using thermodynamics and energy conservation principles.

Let us consider the blood flow through a branched circular arterial tube of internal radius a under an axial transient inertial force f, where (r, θ, z) is a set of cylindrical polar coordinates with the z-axis coinciding with the axis of the tube. Taking a small fluid element near the inner tube wall at a branch point where $r = a$ and $z = 0$, the kinetic energy of the element E_k is $\frac{1}{2}\cdot\rho\cdot V\cdot u_l^2$, where ρ is the density of the fluid, V is the volume of the element, and u_l is the velocity vector of the element. If an initial lesion occupies the element, E_k becomes the kinetic energy of the lesion. This lesion is characterized by volume V, axial adhesive length of the lesion on the endothelium L_a, contact area between the lesion and the endothelium A, surface free energy γ_{sl}, velocity vector u_l, and interfacial shear resistance F_a that is the force resisting the movement of the lesion (Fig. 1). All symbols of the paper are denoted in the nomenclature.

2.2. Energy equation

The adherence of an initial lesion on a plasma–endothelial interface can be treated as a thermodynamic problem in a mixing system because thermodynamics deals with macroscopic and statistical behaviors of interfaces rather than with details of their molecular structures. Surface energy of adhesion E_{sl}, one of thermodynamic terms, is the energy that is required to bring LDL from the interior of the plasma fluid onto the arterial endothelium and form an interface. Blood flow is to obey the principles of conservation of energy, mass, and momentum.

Consider a lesion under an axial transient inertial force f (Fig. 1). Based on thermodynamics and energy conservation principles, the energy equations for the lesion are created as

$$E_k = \frac{1}{2}\cdot F_a\cdot L_a\cdot A, \tag{1}$$

$$E_{sl} = \frac{1}{2}\cdot F_a\cdot L_a, \tag{2}$$

$$E_k = E_{sl}\cdot A, \tag{3}$$

where $E_{sl} = \gamma_s + \gamma_l - \gamma_{sl}$ [30].

Eq. (1) describes the equivalence between the kinetic energy of a lesion E_k and the work done by the total interfacial shear resistance $F_a\cdot A$ along the adhesive length L_a. Eq. (2) represents the equivalence between the surface energy of adhesion E_{sl} and the work done by F_a at a liquid–solid interface. Substitution of Eq. (2) into Eq. (1) yields Eq. (3).

If E_k is greater than $E_{sl}\cdot A$, then the lesion will not form because the kinetic energy of the lesion E_k overcomes the total energy of adherence $E_{sl}\cdot A$ before the adherence of the lesion can occur.

3. Dynamic boundary value model

3.1. Governing equation

Studies of hemodynamics [21–23,28,31–35] suggest that atherosclerotic lesions are located in regions of reduced shear stress of the fluid, which is often associated with flow separation and turbulence. A transient boundary layer, led by the flow, occurs in these regions. The studies also indicated that blood flow near inner arterial walls consists mainly of plasma fluids.

In the dynamic model, the plasma viscous flow in the transient boundary layer near the inner tube wall at an arterial branch point is investigated because lesions arise from this layer. Since plasma fluid is known to be Newtonian, the flow is governed by the Navier–Stokes equation. The following restrictions are imposed to simplify the dynamic model.

1. The plasma may be treated as an incompressible, homogenous fluid.
2. The flow is laminar.

Let us consider an incompressible laminar flow through a circular tube. The governing equation is

$$\rho\cdot\frac{du}{dt} = F_e - \text{grad } P + \mu\cdot\nabla^2\cdot u, \tag{4}$$

where u is the velocity vector of the fluid, F_e is the body force vector, P is the pressure vector, μ is the viscosity of the fluid, ρ is the density of the fluid, and $\mu\cdot\nabla^2\cdot u$ is the viscous force.

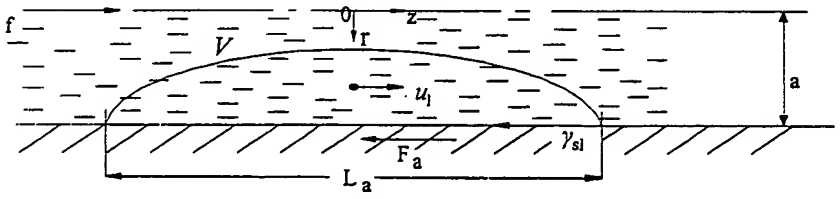

Fig. 1. Axial cross-section of a lesion called a fatty streak adhered on the arterial endothelium.

3.2. Assumptions

The following assumptions are imposed to simplify the boundary value model.

1. The gravitational potential in the fluid has a negligible effect because the transient boundary layer is thin.
2. The rate of flow is steady, and there is a constant pressure flow.
3. The flow does not slip at the inner wall of the tube.
4. The length of the tube is long compared to the region being studied, so that edge effects become negligible.
5. The diameter of the tube does not vary with internal pressure.
6. There is no convection in the flow.

These assumptions and previous restrictions are valid in most studies of hemodynamics [28,35,36].

3.3. Simplified governing equation

Let us use the same notations and consider an incompressible plasma flow in a circular arterial tube with ranges $(a-h(z)) \leqslant r \leqslant a$, $0 \leqslant \theta \leqslant 2\pi$, and $-\infty < z < \infty$, where $h(z)$ is the thickness of the transient boundary layer. Using cylindrical polar coordinates (r, θ, z), we yield $\mu \cdot \nabla^2 \cdot u = \frac{\mu}{r} \cdot \frac{\mathrm{d}}{\mathrm{d}r}\left(r \cdot \frac{\mathrm{d}u_z}{\mathrm{d}r}\right)$, where u_z is a function of r only.

Following the above assumptions, Eq. (4) is simplified to

$$f = \frac{1}{r} \cdot \frac{\mathrm{d}}{\mathrm{d}r}(\tau_{rz} \cdot r) \tag{5}$$

and

$$\tau_{rz} = -\mu \cdot \frac{\mathrm{d}u_z}{\mathrm{d}r}, \tag{6}$$

where u_z is the axial velocity component of the plasma fluid, τ_{rz} is the axial viscous shear stress of the fluid, and f is the axial transient inertial force.

3.4. Boundary condition

According to previous assumptions, the boundary conditions of the model are

$$u_z = 0 \quad \text{at } r = a, \tag{7}$$

$$\tau_{rz} = F(z) \quad \text{at } r = a, \tag{8}$$

where $F(z)$ is the shear force acting on the inner wall of the tube.

If a fatty streak appears at $r = a$ and $z = 0$, we can substitute $F(z) = F_a$ into Eq. (8) to yield

$$\tau_{rz} = F_a \quad \text{at } r = a,\ z = 0, \tag{9}$$

where the interfacial shear resistance F_a is defined in the previous model. Through Eq. (9), we can now join the thermodynamic model and the boundary value model.

3.5. Compatibility condition

As stated previously, there is often separation and turbulent flow at the location of atherosclerosis. The flow at these sites consists of two different types. The first is the plasma flow in the transient boundary layer that is governed mainly by the viscous force. The second is the blood flow in the rest of the regions of the tube that is governed by the axial transient inertial force. Hence, the viscous force and the transient inertial force must equal at the border of the layer for a unique analytic solution. The compatibility condition is created as

$$\tau_{rz} = f_h \quad \text{at } r = a - h(z), \tag{10}$$

where f_h is the axial transient inertial force per unit area. We may take $f_h = f \cdot (a - h(z))$.

3.6. Analytical solutions

Eqs. (5) and (6) combined with Eqs. (7), (8) and (10) yield the axial shear stress of the plasma fluid τ_{rz}, the axial velocity component u_z, and the compatibility equations. (Detailed derivations are omitted due to limited space.)

$$F(z) = f \cdot \left(a - h(z) + \frac{h(z)^2}{2a}\right), \tag{11}$$

$$u_z = \frac{f}{4\mu} \cdot (a^2 - r^2) + \frac{f}{2\mu} \cdot (a - h(z))^2 \cdot \ln\left(\frac{a}{r}\right), \tag{12}$$

$$\tau_{rz} = \frac{f}{2r} \cdot (a - h(z))^2 + \frac{r \cdot f}{2}. \tag{13}$$

Substitution of $F(z) = F_a$ into Eq. (11) yields

$$F_a = f \cdot \left(a - h(z) + \frac{h(z)^2}{2a}\right). \tag{14}$$

Substitution of Eq. (2) into Eq. (14) yields

$$E_{sl} = \frac{1}{2} \cdot L_a \cdot f \cdot \left(a - h(z) + \frac{h(z)^2}{2a}\right). \tag{15}$$

3.7. The effects of turbulence eddies on atherosclerosis

Turbulence eddies do not originate in the transient boundary layer, however, these eddies may enter the layer from the side $r < (a - h(z))$ [37,38]. If we consider the effect of the eddies in the layer on atherosclerosis, the thickness of the layer $h(z)$ in the region near the branch point can be expressed approximately as

$$h(z) \approx B \cdot v_e, \tag{16}$$

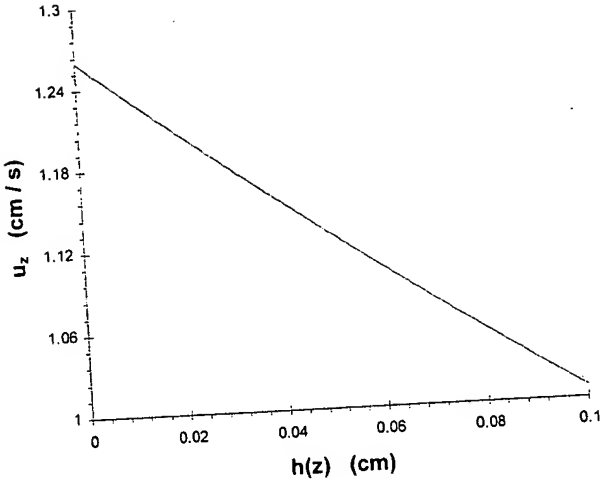

Fig. 2. The relationship between the axial velocity of the plasma fluid and the thickness of the transient boundary layer.

where eddy velocity v_e is a weak function of z and varies with r. Parameter B is determined by the axial velocity u_b of the plasma fluid at the border of the layer and the axial distance z_h between the point being studied and the starting point in the layer.

The transfer of macromolecules in the fluid to a liquid–solid interface may be closely related to v_e. Eq. (16) indicates that increased $h(z)$ involves increased v_e, which implies that LDL in the plasma fluid is more likely to be drawn onto the endothelium. Increased thickness of the transient boundary layer $h(z)$ and increased eddy velocity v_e in regions of the arterial branch points are risk factors in atherogenesis.

4. Conclusions

4.1. Analytical example

We can obtain representative results using some average numbers for a human abdominal aorta vessel [28] by taking the mean internal radius of the vessel $a = 0.5$ cm, mean transient axial velocity $\bar{u} = 15$ cm s^{-1}, mean transient frequency $\omega = 2$ Hz, density $\rho = 1.0$ g cm^{-3}, plasma viscosity $\mu = 1.2$ g s^{-1} cm^{-1}, adhesive length $L_a = 0.2$ cm, and the range of the thickness of the transient boundary layer $0 \leqslant h(z) \leqslant 0.1$ cm. Since $f = \rho \cdot \omega \cdot \bar{u}$, we obtain the axial transient inertial force $f = 30$ g cm^{-2} s^{-2}. Substitutions of $a = 0.5$ cm, $\mu = 1.2$ g s^{-1} cm^{-1}, $f = 30$ g cm^{-2} s^{-2}, $r = 0.4$ cm into Eq. (12) yield Fig. 2 for the boundary value model. Substitutions of $a = 0.5$ cm, $f = 30$ g cm^{-2} s^{-2}, $L_a = 0.2$ cm into Eq. (15) yield Fig. 3 for the thermodynamic model.

4.2. Conclusions

(1) From Eq. (6), Figs. 2 and 3, we find that the shear stress of the plasma fluid τ_{rz} is proportional to the surface energy of adhesion E_{sl} and inversely proportional to the thickness of the transient boundary layer $h(z)$. This means that reduced τ_{rz} results in increased $h(z)$ and reduced E_{sl}.

(2) Fig. 3 and Eq. (16) indicate that increased $h(z)$ involves reduced E_{sl} and increased eddy velocity v_e. Increased $h(z)$ in regions of the arterial branch points is a dominant factor in the formation of initial lesions because, based on both of the previous models, reduced E_{sl} and increased v_e lead to atherosclerosis more easily.

(3) Clinical and experimental results [21–23,28] suggest that atherosclerosis occurs in regions of reduced τ_{rz}. According to Con. 1 and Eq. (16), reduced τ_{rz} involves reduced E_{sl} and increased v_e. This suggests that LDL in the fluid is more prone to be drawn onto the plasma–endothelial interface, and initial lesions form more easily in regions of reduced τ_{rz}.

(4) Clinical and experimental results [31–35] show that locations of atherosclerosis are associated with flow separation and turbulence. Based on Con. 1 and Eq. (16), lesion formation occurs at these locations because it is stimulated by increased $h(z)$ and v_e.

(5) Clinical results [5,24] show that no endothelial defects occur during the formation of initial lesions. According to Con. 1 and Eq. (2), reduced τ_{rz} involves reduced interfacial shear resistance F_a, and since endothelial defects are closely dependent on F_a [21–23], a lower F_a value in the lesion formation area than those of its neighboring sites is therefore not the cause of endothelial defects initially.

(6) Clinical results [3–5] show that atherogenesis is caused by depositions of LDL on the arterial endothe-

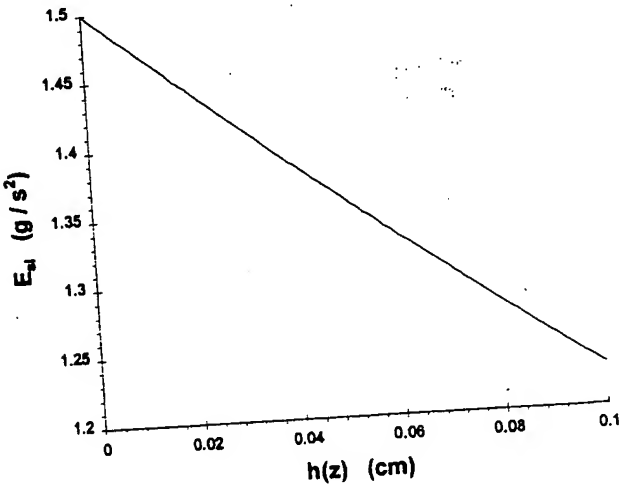

Fig. 3. The relationship between the surface energy of adhesion and the thickness of the transient boundary layer.

lium. According to the thermodynamic model and Eq. (3), LDL rather than HDL (high-density lipoproteins) are drawn from the interior of the plasma fluid onto the plasma–endothelial interface because the lower density of LDL yields a lower E_{sl} than the E_{sl} for HDL deposition. Therefore, reduced E_{sl} and less energy required for LDL deposition leads to atherogenesis.

(7) Clinical results [4,5,28,35] show that initial lesions do not appear in veins and capillary vessels even though there is a lower τ_{rz} in veins than there is in arteries. This phenomenon can be explained by the lack of a transient boundary layer in veins and capillary vessels. The presence of a transient boundary layer is important to initial lesion formation.

5. Mechanism of atherosclerosis

The above conclusions propose that locations of atherosclerotic lesions are associated with regions of increased transient boundary layer $h(z)$ and reduced surface energy of adhesion E_{sl}, which lead to atherogenesis in only a small region of the vast systems of blood vessels. Analytical results of both models predict that increased eddy velocity v_e and reduced E_{sl} in these regions of the arterial branch points are main causes for the formation of initial lesions.

More specifically, increased $h(z)$ in regions of the arterial branch point is responsible for increased v_e and reduced viscous shear stress τ_{rz}. Reduced E_{sl} and increased v_e contribute to bring LDL from the interior of the plasma fluid to the plasma–endothelial interface, which lead to the formation of a lesion. The LDL then passes through the arterial endothelium and stimulates monocytes to enter this area. The monocytes may then engulf cholesterol, and the lesion progresses to a more advanced stage.

6. Discussions and prospects

In this paper, the viscous flow of the plasma fluid in an arterial vessel is characterized by using symbols u_z, τ_{rz}, $h(z)$, v_e, a, f, γ_l, μ, and ρ. The plasma–endothelial interface is characterized by using symbols E_{sl}, γ_s, γ_{sl}, F_a, L_a, and A. An initial lesion is characterized by using symbols ρ, V, E_k, E_{sl}, γ_{sl}, u_l, A, and L_a. The interfacial shear resistance is characterized by using symbols F_a, L_a, and A. The interactions among the plasma flow, interfacial shear resistance, and endothelial cells at a plasma–endothelial interface are investigated using Eqs. (1)–(16). Analytical results show that atherosclerosis and endothelial defects are closely dependent on $h(z)$, E_{sl}, v_e, and F_a. Increased thickness of the transient boundary layer $h(z)$ and reduced surface energy of adhesion E_{sl} are controlling factors in atherogenesis.

The conclusions given by this study offer some insight to the understanding of the fundamental behaviors of atherosclerosis. These conclusions are supported by clinical and experimental results [3–5,21–23,28,31–35], which indicate that the analytical method used is successful as a potential tool in the study of atherosclerosis and other human lesions. This approach may help studies in the effects of interfacial shear resistance F_a and shear stress of the fluid τ_{rz} on the molecular biology of endothelial cells, LDL accumulation, molecular permeability, stress-sensitive gene expression, and signal transduction.

Future works also include:

1. Investigating the intermediate lesions in transition between the fatty streaks and fibrous plaques using analytical methods because these lesions represent the critical stage in the acceleration of atherosclerosis.
2. Analyzing the effects of turbulence eddies on atherosclerosis because the transfer of macromolecules from the interior of the blood fluid into the arterial endothelium are closely dependent on these eddies.

These works will enable us to study environmental, dieting, lifestyle, high blood pressure, exercise, and genetic factors associated with atherosclerosis when the reward of prevention and the potential for regression is maximal.

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